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Frank J. Uxa
Stout, Uxa, Buyan & Mullins, LLP
Suite 300
4 Venture
Irvine, CA 92618

EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,434	GIL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1 March 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed 1 March 2004 has been entered. Applicant has cancelled claims 1 – 44; claims 45 – 67 are pending and under examination.

Claim Objections

2. Applicant is advised that should claim 46 be found allowable, claim 62 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 45 – 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering an agent to a patient, does not reasonably provide enablement for methods of treating pain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

Claim 45 is drawn to a method of treating pain by administering agents comprising a therapeutic component and a targeting component, wherein the targeting component preferentially recognizes alpha-2B adrenergic receptors. Dependent claims are drawn to agents with cytoplasmic translocation components (claim 47), specific targeting components (claim 48),

specific types of pain (claims 46 and 62 – 67), specific toxins (claims 49 – 50), and specific doses and routes of administration (claims 51 – 61). The specification discloses agents wherein a targeting moiety is linked to botulinum toxin A, and contemplates that said agents would be useful in the treatment of pain. However, no data are presented to indicate that the agents in fact alleviate pain in humans or nociceptive responses in animals. Although the specification discloses, for example, on p. 8 of the specification, that the agents *may* be useful in for treating pain, and provides a general protocol for administering a drug to a patient on p. 10, line 30 – p. 11, line 16, applicant does not indicate that the agents disclosed herein alleviate pain. The prior art teaching of Maze et al. (2000. Anesthesiology 92:934-936) indicates that understanding the mechanisms of pain is complex and that findings in one class of mammals does not necessarily apply to others (see p. 935, final paragraph).

The specification discloses (p. 6, lines 18 – 31) that botulinum toxin prevents the release of neurotransmitters from neurons. Therefore, a neuron that has been exposed to botulinum toxin will fail to function effectively (i.e. it will not release its neurotransmitters). This is particularly true of cholinergic neurons (see Physician's Desk Reference entry for BOTOX, p. 1, clinical pharmacology, which indicates that botulinum toxin prevents the release of acetylcholine-containing synaptic vesicles); the specificity of botulinum toxin for cholinergic neurons is due to its affinity for a cell-surface binding site (see Foster et al., U.S. Patent 5,989,545, cited on the information disclosure statement, specifically column 6 lines 58 – 60). Foster et al. teach that when clostridial neurotoxins are coupled to targeting moieties, a novel agent is produced that will inhibit release of a neurotransmitter, thereby effectively allowing one to target the toxic properties to any neuron. The specificity is provided by the interaction between the binding site and the targeting moiety (see column 6, line 65 – column 7, line 25).

The prior art teachings of Eisenach et al. (1996. Anesth Analg 82:621-626) indicate that painful stimuli lead to increased release of norepinephrine, which in turn causes the release of acetylcholine causes analgesia (i.e. alleviates pain); see particularly abstract and p. 624. The prior art teachings of Sawamura et al. (2000. Journal of Neuroscience 20:9242-9251) indicates that the alpha2B adrenergic receptor is required for analgesic effects of nitrous oxide (see p. 9247 and 9250, final paragraph). Animals that lack alpha2B adrenergic receptors do not show the anti-nociceptive effects of nitrous oxide. Sawamura et al. also indicate that blocking the expression of alpha2C adrenergic receptors with antisense oligonucleotides attenuates the anti-nociceptive effects of other pain-relieving agents (see p. 9250, first column). Clearly in order to

treat pain one of skill in the art would choose an agent that either is an agonist of adrenergic or cholinergic neurons. The specification does not disclose whether or not the disclosed agents alleviate pain. In the absence of data or even prophetic examples, the examiner must rely on the prior art teachings to determine if the claims are enabled.

As detailed above and disclosed in Foster et al., a clostridial neurotoxin such as botulinum toxin A, when coupled to a targeting moiety, will inhibit the release of neurotransmitter from those neurons to which it is targeted. In the instant case, a moiety that targets botulinum toxin A to neurons expressing alpha-2B adrenergic receptors will inhibit release of neurotransmitter from those cells. But since alpha-2B adrenergic receptors are required for anti-nociception, preventing neurotransmission in cells that contain them would clearly increase the effects of painful stimuli. One of ordinary skill in the art would expect that the agents described herein would act as *antagonists* of alpha2B adenoceptors as they bring a toxin to cells expressing the relevant receptors, although the teachings of Sawamura et al. indicate that *agonists* of alpha2B or 2C are required for the relief of pain. Sawamura et al. indicate that while the prior art had suggested that other receptors might be involved in pain sensation, the development of mice with targeted mutations allows for clarification of conflicting data in the prior art (see the paragraph spanning pp. 9249 – 9250). Clearly one of ordinary skill in the art would not use the agents disclosed herein to relieve pain.

Claims 45 – 47 and 49 – 67 are broad, in that they are drawn to an agent which comprises any therapeutic component. However, the specification discloses a single class of therapeutic compenents, i.e. those derived from botulinum or tetanus toxins. There is no guidance or direction in the specification as to what may constitute a therapeutic component, and there are no working examples of the administration of any agents showing whether or not they treat pain. Because of the breadth of the claims, the complex nature of the invention, and the lack of guidance given by the specification, even if applicant had shown that botulinum toxin coupled to a targeting moiety were effective in treating pain, claims 45 – 47 and 49 – 67 would not be enabled in their full scope as they are drawn to a broad class of agents limited by neither structure nor function.

Claims 45 – 59 and 61 – 67 are also not enabled for their full scope, insofar as they are drawn to "a therapeutically effective amount of an agent to alleviate pain". It is acknowledged that it would be possible to determine whether or not an agent is effective in alleviating pain. However, since the claims are drawn to an especially toxic agent, certain additional

considerations apply which would require undue experimentation on the part of a skilled artisan. The specification discloses that botulinum toxin is very toxic, and that the LD50 in humans is about 150,000 pg (150 ng). Claims 45 – 59 and 61 - 67 are drawn to systemic, rather than local intramuscular, administration of botulinum toxin. The Physician's Desk Reference entry for botulinum toxin type A indicates that "sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness" and includes a warning that the recommended dose should not be exceeded. The Physician's Desk Reference also teaches specific examples where botulinum toxin A was administered either intramuscularly (mean dose1.25 – 2.5 U or 236 U, depending on the application), or intradermally (50 U), but does not indicate if these doses are effective in alleviating pain. Therefore, undue experimentation would have to be taken in order to determine a dose that is both non-lethal and effective in alleviating pain.

The nature of the invention, treating pain with botulinum toxin, is complex. The claims are broad as they recite few, if any, functional or structural limitations. There are no working examples in the specification concerning methods of treating pain by administering the agents, and no guidance is given as to how to determine an effective dose of the toxin. Furthermore, the prior art indicates that agents which disable neurons expressing alpha2B or 2C adrenergic receptors are likely to worsen, not attenuate pain. Therefore, undue experimentation would be required to practice the methods commensurate in scope with the claims.

5. Claims 45 – 67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to methods of treating pain with therapeutically effective amounts of agents comprising a therapeutic component and a targeting component. Claims 47 – 53 are dependent claims further drawn to a translocation component. With the exception of claim 48, the claims do not recite any structural limitations for the targeting component. One of ordinary skill in the art could not at once envision all the possible chemicals, from nucleic acids to small organic molecules, polypeptides, and antibodies, for example, that could be targeting components. Furthermore, as far as the therapeutic component is concerned, there is no

functional limitation, with the exception of claims 48 – 53, for what the therapeutic agent should do. While claims 50 – 53 recite a specific botulinum toxin, claim 45 - 47 and 54 – 67 either do not require a specific toxin, or only require that the toxin be part of a botulinum toxin, without specifying what part of which toxin should be used. The specification discloses (p. 5) that there are at least six types of botulinum toxin. Similarly, there is no structural or functional limitation for the translocation component in claims 47 - 49 and 54 – 67. The instant disclosure does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

Furthermore, claims 45 – 67 are drawn to therapeutically effective amounts of the agent. The Physician's Desk Reference indicates that very low dosages (1.25 U) can cause paralysis of muscles (p. 11) but there is no guidance as to what constitutes a therapeutically effective does for treating pain, nor is there any disclosure of how pain relief is to be measured. It is acknowledged that claims 51 and 52 recites specific dosages, in terms of units of botulinum toxin, that are to be administered. However as these claims are not limited by route of administration they are sufficiently broad to include, for example, intravenous injection of up to about 300 U (claim 51) or even 500 U (claim 52), the art teaches that 1.25 units can paralyze muscles and by applicant's own admission as little as 3000 units is expected to kill half the people who receive such a dose, these dosages appear to be divorced from any meaningful measure of therapeutic efficacy.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 45 – 46, 54, and 60 – 66 are rejected under 35 U.S.C. 102(e) as being anticipated by Chow et al. (U.S. Patent 6,313,172, issued 6 November 2001, filed 13 April 2000).

The applied reference has a common asignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to methods of treating pain by administering agents which comprise a therapeutic component and a targeting component that is specific for alpha 2B adrenergic receptors. Chow et al. teach several compounds, disclosed in column 3, that activate alpha 2B receptors (see column 3, lines 66 – 67). Chow et al. also teach that their compounds are therapeutic, i.e. they relieve chronic pain (see Example 5). Therefore the compounds are both targeting components and therapeutic components, and the teachings of Example 3 of the '172 patent meet the limitations of claims 45, 46, and 62.

Claims 54, 60, and 61are drawn to specific routes of administration of the agents. The same routes of administration are taught by Chow et al. (column 4, lines 25 – 27).

Claims 63 – 66 of the instant application are drawn to treatment of specific types of pain. Treatment of the same types of pain are claimed in claims 7 – 10 of the '172 patent and are disclosed in examples 6 – 8. Furthermore the disclosure of the '172 patent indicates that

chronic pain includes referred pain, visceral pain, and neuropathic pain (column 5, lines 25 – 28). Therefore the teachings of Chow et al. meet the limitations of instant claims 63 – 66.

8. Claim 47 is rejected under 35 U.S.C. 102(e) as being anticipated by Chow et al. as evidenced by Gordon (U.S. Patent 3,939,145). Claim 47 is a dependent claim from claim 45; the reasons why the '172 patent anticipates claim 45 are provided above. Claim 47 is drawn to an agent further comprising a translocation component. Both claims 1 and 4 of the '172 patent recite structures that comprise hydroxyl (-OH) groups. Gordon teaches (column 6, line 64 – column 7, line 4) that hydroxyl groups aid in the transport of agents into cells, and therefore constitutes a translocation agent as defined by applicant (see specification, p. 15, lines 28 – 30). Applicant has stated that a translocation component can be from the same molecule as a therapeutic component (specification, p. 10, lines 35 – 36).

9. Claim 45, 46, 62, and 66 are rejected under 35 U.S.C. 102(b) as being aniticipated by Campbell (U.S. Patent 5,447,947, issued 5 September 1995, filed 25 June 1992), as evidenced by de Vos et al. (1992. J Neurochem 58:1555-1560). Claim 45 is drawn to a method of treating pain by administering an agent comprising a therapeutic component and a targeting component, wherein the targeting component binds at alpha 2B or 2C adrenergic receptors. Dependent claims 46, 62, and 66 are drawn to specific types of pain. Campbell teaches prazosin is useful for treating sympathetically maintained pain ("SMP"; see column 2, lines 22 – 23), and de Vos et al. teach that prazosin binds with high affinity to alpha-2B and 2C adrenergic receptors (p. 1555, first paragraph, and p. 1559, the paragraph beginning on p. 1558). Prazosin is both the therapeutic component and the targeting component, therefore the teaching meets the limitation of claim 45. Campbell teaches that SMP is a form of chronic pain and also comprises allodynia (column 1, lines 18 – 36). Therefore since prazosin is effective in treating SMP, and SMP constitutes both chronic pain and allodynia, the teachings of Campbell also meet the limitations of claims 46, 62, and 66.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 45 – 47, 49 – 50, 54, 56 – 64, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (U.S. Patent 5,989,545, cited on the information disclosure statement), in view of Unger et al. (U.S. Patent 6,139,819, issued 31 October 2000, filed 17 September 1997), de Vos et al. (1992. J Neurochem 58:1555-1560), Campbell (U.S. Patent 5,447,947, issued 5 September 1995, filed 25 June 1992), and Dolly et al. (WO 95/32738, cited on the information disclosure statement). Foster et al. teach methods of treating pain by administering agents which comprise clostridial toxins as therapeutic components coupled to targeting components.

Foster et al. teach that their methods are useful for the treatment of chronic pain (column 1, lines 11 – 13), meeting the limitations of claims 46 and 62. Foster et al. teach using a linker molecule that affects internalization (i.e. translocation, see column 7, lines 58 – 63) of the agent, meeting the limitations of claim 47. Foster et al. also teach that the light chain of a clostridial toxin can act as an translocation component (column 7, lines 5 – 10), and teach that C. botulinum can be used as the source of the clostridial toxin (column 6, lines 35 – 37), meeting the limitations of claim 49. Foster et al. teach that type A toxin can be used (column 6, line 39), meeting the limitations of claim 50. Foster et al. also teach that the agent can be administered intrathecally at any level of the spinal column (column 8 line 54 – 58), thereby meeting the limitations of claims 54 and 56 – 59. Foster et al. also teach that the compound can be administered locally into a region experiencing pain (column 8, lines 44 – 53), which could be either intramuscularly or subcutaneously, meeting the limitations of claims 60 and 61.

Foster et al. teach that chronic pain includes allodynia associated with neuropathic pain (column 2 lines 58 – 62), thereby meeting the limitations of claims 64 and 66. Foster et al. also teach that the agents can be administered spinally at the level of the incoming afferent of an affected organ (column 14, claim 43) and teach that fibers from the viscera enter the spinal cord (column 2, lines 3 – 15). Thus the teachings of Foster also meet the limitations of claim 63.

Foster et al. list several agents which could comprise the targeting component (see column 12), but Foster et al. do not teach a component that preferentially binds to alpha 2B or 2C adrenergic receptors.

Unger et al. teach compounds wherein contrast agents for MRI are targeted to cells by linking said agents to targeting components. A specific preferred embodiment of Unger et al.'s invention is using prazosin as the targeting agent (see column 38, lines 53 – 67).

De Vos et al. teach that prazosin binds with high affinity to alpha-2B and 2C adrenergic receptors (see de Vos et al., particularly p. 1555, first paragraph, and p. 1559, the paragraph beginning on p. 1558).

Campbell teaches prazosin is useful for treating pain (column 2, lines 22 – 23).

It would have been obvious to one of ordinary skill in the art to make a pain-relieveing agent that comprises botulinum toxin as the therapeutic component and prazosin as the targeting component, and to administer it to a mammal with a reasonable expectation of success. Both prazosin and clostridial toxins are useful for treating pain, and it is *prima facie* obvious to combine two products which is each useful for the same thing (see MPEP 2144.06). Furthermore Dolly et al. teach methods of coupling any drug to a clostridial toxin (see p. 14 - 18), and teach that such compounds are useful for treating pain (see p. 3, line 16).

13. Claims 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster, Unger, De Vos, Campbell, and Dolly as applied to claim 50 above, and further in view of Simpson et al. (1996. Neurology 46:1306-1310). Neither Foster, Unger, De Vos, Campbell, or Dolly teach specific doses of the botulinum toxin. Simpson et al. teach the administration of doses ranging from 75 – 300 units are effective in alleviating spasticity (see table 2, p. 1308). Spasticity leads to pain (p. 1306, end of first paragraph). It would have been obvious to one of ordinary skill in the art to use any of the doses shown to be effective in spasticity relief and pain. The motivation would be to use a dose of the toxin effective in relieving pain, and Simpson et al. teach this is beneficial to patients (p. 1309, second column, second complete paragraph).

14. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Foster, Unger, De Vos, Campbell, and Dolly as applied to claim 50 above, as evidenced by Dauer et al. (1998. Brain 121:547-560). Foster, Unger, De Vos, Campbell, and Dolly do not teach pain relief lasting from about 2 to about 27 months. Dauer et al. teach pain relief lasting an average of 12 weeks after botulinum toxin injection (p. 554 first complete paragraph). It would have been obvious for

one of ordinary skill in the art to relieve pain for between 2 and 27 months. The duration of the pain relief is an inherent property of the toxin, and would be accomplished by administering it.

15. Claim 65 is rejected under 35 U.S.C. 103(a) as being unpatentable over claim Foster, Unger, De Vos, Campbell, and Dolly as applied to claim 63 above, as evidenced by Kandel et al. (1991. Principles of Neural Science, 3rd edition, p. 389, first column, 4th paragraph). Foster, Unger, De Vos, Campbell, and Dolly do not teach relief of referred pain. Kandel teaches that referred pain arises from visceral pain but is felt elsewhere. Treating visceral pain will inherently treat referred pain.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 45, 46, and 62 – 66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4 - 10 of U.S. Patent No. 6,313,172, issued to Chow et al. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

1) The structure listed in claim 1 of the '172 is generic, as is the structure listed in claim 48 of the instant application. The R groups, as defined in both the '172 patent and the instant specification and claims, have sufficient overlap that the two structures are not patentably

distinct. Although the above structure is recited in claim 48 of the instant application to be a targeting compound, claim 1 of the '172 patent is drawn to a method of treating pain by administration of that structure alone. Clearly the structure is sufficient both to treat pain *and* to serve as an alpha2B adrenergic targeting component.

2) The structure listed in claim 4 of the '172 patent is a species of the generic structure listed in claim 48 of the instant application, wherein:

X is R4-C=C-R5

R1 and R3, R4, and R5 are H

R2 is F

The specification discloses that by using this definition of X, the 5-membered ring becomes a 6-membered ring, with a double bond (p. 9, lines 3 – 4). Although the above structure is recited in claim 48 to be a targeting compound, claim 4 of the '172 patent is drawn to a method of treating pain by administration of that structure alone. Clearly the structure is sufficient both to treat pain and to serve as an alpha2B adrenergic targeting component.

Claim 45 is drawn to a method of treating pain by administering an agent comprising a targeting component and a therapeutic component. Dependent claims 46, and 62 – 66 are drawn to treatment of specific types of pain and to treatment with an agent that further comprises a translocating moiety. Nowhere in either the specification or the claims is there an explicit requirement that the targeting and therapeutic components be separate moieties. In fact, applicant has quite clearly acknowledged that a single moiety can serve two roles within the agent. On page 10, lines 35 – 36, applicant states that a therapeutic component and a translocation component can be found together in a botulinum toxin. Using the same logic, a therapeutic component and a targeting component can both be found together in a single moiety, for example the structures listed in claims 1 and 4 of the '172 patent. Chow et al. teach that their agents specifically bind alpha2B adrenergic receptors (column 3, lines 66 – 67), and the claims of their patent are drawn to methods of treating pain by administering their agents. The method in claims 1 and 4 of the '172 patent are not distinct from the methods in claim 45 of the instant application. Similarly, the methods in claims 6 – 10 of the '172 patent are not distinct from claims 46 and 62 – 66 of the instant application, as all are drawn to methods of treating the same specific types of pain.

18. Claim 47 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4 of U.S. Patent No. 6,313,172 in view of

Gordon (U.S. Patent 3,939,145). Claim 47 is a dependent claim from claim 45; the reasons why the '172 patent constitute an invention that is not patentably distinct are provided above. The claim is drawn to an agent further comprising a translocation component. Both claims 1 and 4 of the '172 patent recite structures that comprise hydroxyl (-OH) groups. Gordon teaches (column 6, line 64 – column 7, line 4) that hydroxyl groups aid in the transport of agents into cells, and therefore constitutes a translocation agent as defined by applicant (see specification, p. 15, lines 28 – 30). Applicant has stated that a translocation component can be from the same molecule as a therapeutic component (specification, p. 10, lines 35 – 36).

19. Claims 54 – 61 are rejected under the judicially created doctrine of double patenting over claims 4 and 5 of U. S. Patent No. 6,313,172 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Claims 54 – 61 are drawn to methods of treating pain by administering agents via specific routes. The reasons why the instantly claimed methods of treating pain are susceptible to double-patenting rejections are explained above. Claim 5 of the '172 patent is drawn to the oral route of administration. However, the specification of the '172 patent discloses that the methods of treating pain can be accomplished by numerous other routes of administration, including, without exception, intrathecal, intramuscular, and subcutaneous (see column 4, lines 24 – 27). These are the same routes that are recited in claims 54 – 61 of the instant application.

Conclusion

20. No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
March 23, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
5-28-05